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INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON SKELETAL MUSCLE

by

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CONTENTS

INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON SKELETAL MUSCLE.

Section 1.

The Sympathetic Innervation of Skeletal Muscle.

A. Introduction.

It is well known that fibers from the sympathetic nervous system regulate the size of blood vessels in skeletal muscle. Thus, sympathetic fibers are found in skeletal muscle. However, the question of direct sympathetic innervation of skeletal muscle fibers in addition to the somatic innervation of the same or different skeletal muscle fibers, has been the subject of dispute for a number of years. Consequently, the first section of this thesis will be devoted to a brief survey and interpretation of the histological studies of sympathetic innervation of skeletal muscle. At the conclusion of this survey, there will follow a study of the influence which the sympathetic system apparently exerts on skeletal muscle, and a suggestion will be made of the mechanism of this influence in the light of conclusions drawn from the histological survey.

B. The Innervation of Skeletal Muscle Fibers by Sympathetic Nerves.

The idea of direct sympathetic innervation of skeletal muscle originated with the observation by Tschiriev (56) of "terminaisons en grappes" or grape-like endings in addition to ordinary motor endings on the muscle fibers. Also very early, Perroncito (72) stated that ramifying non-medullated fibers of sympathetic origin end on the muscle fibers.

By far the greatest support for this contention arises from the numerous experiments of Boeke. In an early report of his (4), histological sections

of normal tissue of various muscles in embryonic and pre-adult cats, moles, starlings, mice, and lizards, prepared by a silver technique,are shown to exhibit thin, non-medullated, "accessory" fibers: these in some instances run in bundles, in others, singly: in some instances accompany the motor nerve, in others, running independently. Boeke claims that these fibers end hypolemmally in the same sole plate as the motor fiber but in separate end plates of characteristic form; namely, end rings, end loops, and delicate end nets. However, these fibers were not traced centrally, the basis of the sympathetic interpretation being the non-medullated character of the fibers and the presence, in one case, of a branch of an "accessory" fiber supplying a capillary. Boeke later confirmed his results (5), employing additional techniques; and he reiterated his sympathetic interpretation, asserting that the fibers never branch from motor fibers and that they were undegenerated in extrinsic eye musculature after degeneration of the motor nerves as a result of sectioning the trochlear nerve at its base.

In collaboration with Dusser de Barenne, Boeke (6) brought further evidence to bear on the sympathetic character of the "accessory" fibers; and they assigned to them the function of centrifugal transmission of impulses. Using the Bieschowsky technique, they describe bundles of non-medullated fibers ending in the characteristic endings of Boeke and in more complex end plates, in the intercostal muscles muscles of cats a month after the spinal nerve roots were sectioned. All the medullated fibers had disappeared through degeneration.

Agduhr's experiments, however, were more conclusive (1). Five to ten days after the spinal nerve supply to the interosseus muscle of cats had been destroyed on one side of the animals, he observed that medullated nerves were absent and that non-medullated fibers ending on blood vessels and skeletal

muscle fibers were present. Four to six days after the stellate ganglion was removed on the other side of the animals, there was, Agduhr claimed, evidence of degenerated non-medullated fibers. In a report of an experiment similar to Agduhr's spinal nerve degeneration experiment with the addition of sections of the normal tissue, Kuntz and Kerper (58) state that they were able to confirm Boeke, Agduhr, and Dusser de Barenne, using the gold chloride and pyridine silver techniques, but they offer neither drawings nor photographs in support of this contention.

The reports of Kulchitsky (56) are particularly interesting in that they partly support and partly dispute Boeke's contentions. In python muscle he observed non-medullated fibers running from bundles to end on muscle fibers in "terminaisons en grappes" branching endings with numerous small end plates. Contrary to Boeke, however, he states that each muscle fiber is innervated either by a medullated or a non-medullated fiber, not by both; further, that the non-medullated fibers end epilemmally, having no sarcoplasmic granular material, as in the case of motor endings, in the region of the end plate; and he claims that they have no relation to the sympathetic fibers of the blood vessels.

The contention persisted, however, that non-medullated fibers ending on blood vessels and on skeletal muscle fibers could be organized into one system as a part of the sympathetic. Such is the claim of Garven (38) as a result of his work on hedgehog muscle. Here he found "accessory" fibers ending in various places: in the same sole plate as the motor nerve, outside this sole plate in independent end plates, in the walls of the capillaries in the region of the motor end plates, and in plexuses from which fibers ran to the previously named regions. But some doubt is reflected by his statement that at times he could not determine whether the "accessory" fibers were inside

or outside the sheath of Henle. Garven did, however, claim that he could distinguish between the non-medullated branches of motor nerves and the system of sympathetic fibers.

In more recent years, double innervation of the muscle fibers, sympathetic and motor, has been reaffirmed by Boeke (7) in a series of experiments where in one part degeneration of the supposed sympathetic supply to the extrinsic eye muscles was attempted by removal of the cervical sympathetic, and where in another part degeneration of the medullated nerves was effected. As a result of these experiments Boeke altered in no way his previous conclusions (although he found it necessary to interpret non-medullated fibers, remaining on degeneration, as arising from cells in the brain stem rather than from the sympathetic chain).

The consistent results of Boeke seemed to testify to the accuracy of the sympathetic interpretation. His earlier work, alone, is inadequate; for he then failed to offer definite evidence of the origin of the non-medullated fibers observed. But even with the substantiation of his results by Kuntz and Kerper (58) and Agduhr (1), more recent observers have offered very convincing evidence as to the inaccuracy of the sympathetic interpretation.

C. Evidence of the Absence of Direct Sympathetic Innervation of Skeletal Muscle Fibers.

Considerable clarification has been given to the whole question by the work of Wilkinson (101) for two reasons: the consistent results obtained with the employment of several techniques; and the opportunity available for a study of the sections prepared by Boeke, Dusser de Barenne, and Agduhr. In most cases, in his own work on the lizard, he found that the "terminaisons en grappes" are the hypolemmal endings of non-medullated branches of motor

nerves; and these he considers to be "immature" motor endings which he very convincingly arranges in a series representing the various stages of maturity from the simple single bead ending to the most complex, closely resembling an ordinary motor ending. None of these are of sympathetic character as was claimed by Boeke (7). As previously stated, most of the endings are hypolemmal, a fact clearly demonstrated in photographs which show the presence of sole plates; and some that are epilemmal in character are shown to be the endings of non-medullated branches of sensory nerves. Probably the most convincing evidence of the motor character of the "terminaisons en grappes" was the failure to find any other type of motor end plate on the muscle fibers supplied by such a termination, an observation which agrees histologically but not interpretatively with Kulchitsky's (56). Wilkinson applies this entire interpretation, moreover, to the endings in muscle spindles described by Agduhr (1) as sympathetic and by Hines and Tower (48) as somatic. However, in mammals he could find the "terminaisons en grappes" only as epilemmal endings of non-medullated arborizations of a medullated plexus of sensory nerves; a fact further substantiated by the presence on the same muscle fibers of ordinary motor end plates.

Of course, the subjective factor is especially important in the interpretation of fine structures in histological sections; and for this reason Wilkinson's interpretation (101) of the sections prepared by Boeke (7), Boeke and Barenne (6), and Agduhr (1), is particularly interesting. In many instances he was able to trace back "sympathetic" endings, and he found them to be non-medullated branches of motor nerves. In a paper of Tower (92), a similar interpretation is placed on non-medullated fibers found in histological preparations of skeletal muscle tissue from cats, dogs, and goats. The eye muscle preparations of Boeke (7) are criticised both for the short degeneration time

and for the failure to interpret the endings as epilemmal and sensory (Wilkinson states in his criticism, however, that this interpretation error is relatively easy to make in surface preparations). His major criticism of Boeke and Barenne's work (6) is not the observation of "hypolemmal" endings lying loosely in the connective tissue, but rather the failure to control for the possibility of ganglion cells lying peripheral to the point of section of the spinal nerves supplying the intercostal muscles. It is quite possible, as Wilkinson points out, that there are sympathetic fibers in the vicinity of the sole plates, but they probably supply capillary walls of the "confluens capillorum", an anastomosing network of capillaries in close proximity to the sole plate. Then too, capillaries are so intimately associated with the muscle fibers, that nerves supplying the vessels might often appear to supply the fibers (101). The earlier workers were too prone to accept non-medullated fibers with visible nuclei in the neurolemma as sympathetic fibers (Hines and Tower (48) point out that such was thought to be characteristic of sympathetic nerves) when they are probably branches of medullated nerves: also, many observers have failed to prepare normal sections to determine the effect of stains upon them; and in a restriction to a limited number of techniques, often but one, what is merely indistinguishable may be considered absent.

The certainty with which Boeke describes the sympathetic endings in extrinsic eye muscles (7) is further dispelled by repetition of these experiments on cats by Wilkinson (102). He found that Boeke did not allow sufficient time for degeneration of the somatic nerve supply; the motor end plates requiring for degeneration six to seven days; the axonal ramifications, three to five days: and the proprioceptive sensory endings, four to six days. Thus, what Boeke describes as sympathetic endings are, according to Wilkinson, epi-

lemmal proprioceptive endings with the characteristic configurations of Boeke's description and occasionally with formations resembling "terminaisons en grappes". That these endings are sensory is indicated by their epilemmal character and by their longer degeneration time after trochlear nerve section. The continued presence of some proprioceptive endings after long periods of degeneration is explained by the presence in the trochlear nerve of medullated fibers arising in the fifth nerve.

Support is given to the evidence submitted by Wilkinson (102) by the more recent work of Woolard (103). He found that in addition to the motor end plate there are medullated claw-like endings to thick muscle fibers and non-medullated ones to thin muscle fibers. Both types of endings arise from medullated fibers in the ocular nerves. He offers excellent evidence to support his contention that these endings are sensory, with fibers originating in the same part of the brain as the proprioceptive fibers to the muscles of mastication.

In his most recent paper Wilkinson (105) reiterates his previous assertion that the only sympathetic fibers found in skeletal muscle are those found in relation to the blood vessels of the muscle. He produced degeneration of the spinal nerves with their non-medullated branches supplying the intercostal, the interosseus, and the lumbricalis muscles. In sectioning the spinal nerves he made the cuts distal enough to the spinal ganglia to insure that no ganglion cells lying outside the spinal ganglia would be peripheral to the point of section. Even with these precautions the only nerve fibers remaining after degeneration in these experiments on the skeletal muscle of cats, were the sympathetic fibers supplying the blood vessels.

From the more exhaustive or more thorough work in the duplication of

early experiments and the addition of new ones, the evidence seems to indicate that there is no direct sympathetic innervation of skeletal muscle. Although this later evidence seems quite positive in its conclusion, it is well to discuss from a slightly different point of view the innervation in its relationship to an important phase of activity.

D. Single and Double Innervation of Skeletal Muscle Fibers.

In this particular instance, the phrase 'single innervation' is to be understood as meaning the ending of an ordinary motor nerve or sympathetic nerve on a skeletal muscle fiber as distinguished from the phrase 'double innervation' meaning the termination of both sympathetic and motor nerves on this type of muscle fiber. Hunter (52) assigns to the sympathetic nervous system the function of regulating the small thin muscle fibers which supposedly control plastic tonus, and to the somatic nerves the function of regulating the large thick fibers controlling postural tonus. Thus he assigns two types of activity respectively to the two types of nerve and muscle. This assumption of single innervation is supported by evidence of a decrease in the size of some of the muscle fibers on degeneration of the sympathetic supply to the muscle (Hunter and Royle (52)). However, Hay (44) was unable to find any difference in the type of innervation to white and red muscle fibers, observing the same number of motor end plates, afferent fibers and motor fibers per unit bulk of each type of fiber. But Feldberg (31) claims that no change occurs in the size of muscle fibers in ear muscles of rabbits after removal of the sympathetic. From this evidence and from the previous discussion there seems to be no adequate basis for Hunter's assumption, for it is clearly shown that ordinary motor end plates are present in both types of muscle fibers.

In spite, however, of the apparent absence of direct sympathetic innervation of skeletal muscle, physiological experiments seem to indicate a direct influence of the sympathetic system on skeletal muscle. But even this incongruity is understandable in the light of the results of relatively recent research.

Section 2.

The Sympathetic Nervous System and Muscle Tonus.

A. Introduction.

A review of the topic of skeletal muscle tonus would not be apropos in this section, since it is so broad a subject and since it has been often excellently reviewed. Instead, discussion on the topic will be reserved for a brief statement of the fundamental relationship of tonus to the simple stretch reflex. Liddell and Sherrington (88)(20) have shown that even a slight stretch on the muscle acts as a stimulus to produce reflex contractions. This resistance to stretch depends for intensity on the degree of stretching. A continued state of contraction occurs when there is no increase in the degree of stretch tending to produce an increase or augmentation of the reflex contraction. It is to this phenomenon of sustained contraction which has as its basis a simple somatic reflex contraction after stimulation by stretch of the intramuscular receptors, or in other words a simple proprioceptive reflex, that we give the name tonus. In the light of this interpretation, decerebrate rigidity or "reflex standing" is an exaggerated state of tonus where the sustained contraction state is maintained by sets of fibers which alternately contract and relax, the number of sets contracting depending on the tension. To quote Sherrington (87) : "the trend of experimental evidence is to show postural tonus to be simply part and parcel of ordinary motility; a manifestation of that ordinary rhythmic neuro-muscular activity by which are executed all our reflex and other acts involving the skeletal musculature. The tonic i.e. reflex postural form of that activity, because mild and static, involves relatively little expensive metabolism

and is little liable to fatigue."

However, the interpretation of muscle tonus, decerebrate rigidity, and voluntary contraction as involving a common basic type of response, has not always been generally accepted. Muscle tonus and decerebrate rigidity have such distinguishing characteristics that earlier workers sought their explanation in a particular type of nervous organization restricted to these phenomena. The evidence from early experiments directed attention toward the possible influence of the sympathetic nervous system on these phenomena. The work of J.I. Hunter again serves as a convenient dividing line in the discussion, for he renewed the strength of the controversy over the existence of such influence.

B. The Problem Previous to the Time of J.I. Hunter.

The very early investigations of DeBoer (26)(27) reveal a loss of tonus in the limbs of frogs upon sympathetic ramisectomy as indicated by lessening in resistance to passive extension, appearance of flaccidity in the operated limb on walking, and a lower hanging operated limb. Entire removal of the sympathetic chain in cats (20) produced a similar lack of response to various passive movements of the operated limb. However, the photographs submitted are far from convincing. Although DeBoer states, without proof, that circulatory changes on sympathectomy would not be immediate, it seems that some control should have been employed for the possible effect on tonus of a circulatory change, especially where the decrease in tonus was so slight. A similar control was needed for the possible effect of unilateral operative injury on tonus.

Instead of bestowing the control of tonus completely on the sympathetic nervous system, Dusser de Barenne (28), in confirming DeBoer's results, contends that the sympathetic control is only partial since the loss of tonus

on sympathectomy is not so great as the loss on removal of the spinal nerve supply to the limb. Very interestingly he explains the return to normal tone eight weeks after sympathetic chain extirpation in terms of a compensation by the central nervous system without attempting to determine the possibility of circulatory readjustments.

The importance of these experiments lies not in their results, for in both cases there is a lack of adequate controls, but in the fact that the results obtained have stimulated experimentation on this problem, the evidence collected mostly contradicting the earlier experiments. Although Yas Kuno (104), by sympathetic extirpation in frogs, and Van Rijnberk (97), by stimulation of the sympathetic supply to the diaphragm in mammals, were unable to observe any effect on tonus, the most convincing evidence against this sympathetic function of direct tonus regulation is that assembled by Negrin Y Lopez and von Brücke (74), Cobb (19), and Newton (75). The observations of the first named men are important in that, consistently, in a very large number of experiments, they found in frogs only very short periods of atony after sympathectomy, and no effects whatsoever on decerebrate rigidity following the sympathetic removal. Cobb observed no hypotonus after sympathectomy in either normal or decerebrate cats; but here the emphasis will be placed on a statement made by him because of the bearing it has in criticism of later papers: "that slight differences in grasping and holding the cat's neck caused changes in the hanging of the legs and their stiffness; their seemed to be a synergic relation between the position of the neck and the tonus of the hind legs which might explain some of the former observations". The importance of the final paper (75) lies not in its contradiction of DeBoer's results, but rather in the emphasis on the importance of operative procedure. Newton contends that, especially in unilateral operations, with the easy

possibility of peritoneal injury and, in warm-blooded animals, with the danger of cooling surrounded tissue, it is difficult to be certain that the hypotonus is not the result of widespread operative injury.

There are several other reports of contradictions of the work of DeBoer and Dusser de Barenne, but no more will be said about this work (since the evidence is of similar nature to that just discussed) than to mention the names of Takahashi (89), Uyeno (94), and Saleck and Weitbrecht (84). In spite of the wealth of such contradictory evidence, the certainty of the conclusion that the sympathetic has no effect on muscle tone was weakened by the work of Hunter.

C. Hunter's Evidence and Theory of Sympathetic Tonus Control.

The work of Hunter and Royle (50) (51) (82) is really the most outstanding in support of the conception of sympathetic regulation of muscle tonus. As faulty as the conclusions which they drew and the assumptions from which they drew these conclusions might have been, their efforts tended toward eventual clarification of the question of tonus control and its sympathetic relationship by the work it inspired.

Hunter based his experiments and interpretations of results on two major assumptions. The first of these was the idea that two types of skeletal muscle fibers exist having two types of innervation, somatic and sympathetic (51). This question has already been discussed (Section 1). The other assumption is the natural consequence of his belief that the two types of muscle fibers in the higher vertebrates were responsible for two types of activity, just as different muscle groups are found in the invertebrates governing different types of activity. This second assumption invokes two kinds of tonus: plastic, maintaining a part of the body in whatever position it is

placed; and contractile, producing movement of the part. These two types of tonus he allocates to the two types of fibers, thin and thick. From the work of Langelaan (63) Hunter drew his conclusions that the existence of plastic and contractile tonus was a definitely established fact, with the sympathetic system regulating plastic tonus and the somatic, contractile tonus.

The conclusions of Hunter and Royle have foundation in their experimental work on goats and birds (51) (82). With respect to birds, Hunter found that section of the cervical sympathetic cord, with bilateral operation but with unilateral sympathectomy, produced after the operation a drooping of the wing. This loss of plastic tone with contractile tone remaining was also brought about by sectioning the posterior roots of the afferent limb of a sympathetic reflex arc. This so-called plastic tone remained when voluntary movement was made impossible by cutting the last four cervical nerves, only to disappear with a sectioning of the cervical sympathetic chain. Thus, he concludes that two reflex arcs exist subserving tone, a sympathetic arc regulating plastic or fixing tonus, and a somatic arc regulating contractile or active tonus.

A similar effect on tonus was observed by Royle (82) in goats. Here sympathectomy was performed on normal animals, on spinal animals, on animals whose cord was transected, and on animals decerebrated at varying periods after sympathectomy. In all cases a considerable period intervened between the operation of sympathetic removal and the observations of positive results. By passive movements of the limbs and elicitation of reflexes, Royle found that there was a weakening of reflex action (including the lengthening and shortening reactions) and a general drooping of the sympathectomized limbs. One important point to be observed now is that both Hunter and Royle claim that the condition of fixation attained in lengthening and shortening

reactions is a state of plastic tone regulated by the sympathetic nervous system.

The work of Hunter has been confirmed frequently. The more important confirmations of the work on birds are those of G. and F. Popa (77) (78), Van Dijk (96), and Kuntz and Kerper (61). The Popas obtained results similar to those of Hunter, namely, drooping of the wing after sectioning the cervical sympathetic. But very important are their statements that the difference in tonic conditions of the wings persisted after thirty-five months and that the later effect of sympathectomy was an increased sensitiveness to cold. Van Dijk, in duplication of Hunter's experiments by sectioning at first singly the somatic and sympathetic "reflex arcs" and later both arcs, offers support to Hunter, but he observed differences when there was an interval between operation and observation.

By far the most extensive support given to the results obtained by Hunter and Royle in mammals, is that offered by Kuntz and Kerper. In an early paper (57) they indicate the appearance in dogs of a hypotonus of the legs after sympathectomy, a condition of which maximum duration was two weeks. These sympathectomized hypotonic limbs were more easily fatigued, even without the circulation to normal and operated limbs. The hypotonus in a unilaterally sympathectomized limb was confirmed in a later paper (61); and its definiteness was assured with the animals under light anasthesia, because the authors state that in the unanesthetized animal the somatic innervation compensates for loss in tone as a result of sympathectomy, consequently cloaking actual hypotonus. This hypotony appeared in most cases shortly after the operation. Exact measurements of tonus in quadriceps femoris muscles were made by determining th resistance offered to passive flexion of an extended leg, a resistance which the authors term the "brake" phenomenon but which

Fulton (34) shows to be nothing more than a manifestation of the simple muscle twitch in an antigravity muscle. Upon unilateral sympathectomy this "brake"phenomenon disappeared. It would seem then that Kuntz and Kerper confirm the results of Royle on the effect of sympathectomy on the state of fixation or resistance of the lengthening and shortening reactions. In later papers (59) (60), the authors further substantiate their previous work; and throughout, they accept the idea of sympathetic regulation of plastic tonus with compensation by somatic nerves after sympathectomy.

D. Criticism and Contradiction of Hunter's Evidence.

As stated previously, the acceptance by Hunter, Royle, Kuntz and Kerper, etc., of the conception of two types of tonus, plastic and contractile, is based on the work of Langelaan (63). His work has already been thoroughly criticised by Forbes (33) and Cobb (20). It might be added, however, that in a study of the work it seems obvious that there was insufficient evidence from work on the extension curves of the loaded gastrocnemius where, by stimulation of the motor nerve, one reflex contraction was slower than another, for postulating two types of tonus: plastic, observed by compressing the belly of the muscle and regulated in the sarcoplasm by sympathetic nerves; and contractile, a slight state of contraction regulated in the striped apparatus by somatic innervation. Forbes (33) has expressed Sherrington's point of view(and I have quoted a recent statement by Sherrington) that, slow or fast, reflex contractions have as their foundation the simple muscle twitch. Then too, I fear that succeeding workers have broadened their interpretation of the two types of tonus to suit their purposes; namely, where plastic tonus is a form of elasticity according to Langelaan, these workers have assumed it to include what Langelaan might have called contractile tonus.

The contractile tonus of Langelaan has been altered from a state of slight contraction to one of actual movement.

The present idea of closely relating decerebrate rigidity, muscle tonus and the simple muscle twitch, has already been discussed earlier in this section. The use of shortening and lengthening reactions to determine the influence of the sympathetic nervous system on plastic tonus constituted a very important part of the experimental observations of Hunter and Royle. In their opinion,the more or less fixed condition of shortening in the muscles which offered resistance to lengthening, characteristic of the shortening reaction, and the fixed condition of the length of the muscle, characteristic of the lengthening reaction, were made possible by the phenomenon of plastic tonus. However, such an interpretation is unnecessary, as an understanding of the stretch reflex brings out. To quote Fulton (35): "The 'lengthening' and 'shortening' reactions are both reflex in nature, the 'shortening' reaction'being indistinguishable from the stretch reflex, the 'lengthening reaction' being a reflex inhibition brought about by the stimulation of the inhibitory (probably nociceptive) afferents within the muscle. It is evident from this that the plasticity of muscle is explicable in terms of reflex coördination and integration of the all-or-none responses of the individual muscle units, the assumption of special 'fixing' mechanisms being quite unnecessary to account for this property of skeletal muscle." Thus we may safely dispose of the hypothesis of plastic and contractile tonus, for, as Forbes (33) has pointed out, dual function in skeletal muscle demands as a prerequisite two excitable structures since the qualitative variations in the stimulus do not effect the independence of the functional response.

The most serious objection to Hunter's evidence of direct sympathetic influence on tonus is probably the interval of time required to elapse before

the effect of sympathectomy on tonus can be observed. To agree with his claim that this loss was a reflex phenomenon, the loss of tonus should have been immediate on sympathectomy. This is necessary, if we are to accept the loss as being the primary result of sympathetic removal, for immediate results are observable on the effect on voluntary movement of sectioning the somatic nerves controlling movement. This criticism agrees with that of Bailey in his comment on Royle's operation of sympathetic ramisectomy to relieve spastic paralysis (25). The immediate response to sectioning posterior roots in birds obtained by Hunter is indicative of what the response should be to sympathectomy, although his interpretation of the result is no proof that it was not due to a wider spread lesion affecting the somatic reflex arc. Although Hunter describes these immediate effects on birds' wings, others, notably Van Dijk (95), have confirmed his results only when an interval of time has elapsed after the operation. There are in the bird certain anatomical differences in the relationship between sympathetic and somatic nerves that might be considered adequate, without sufficient control, to vitiate the conclusions drawn. For example, Coates and Tiegs (18) clearly show in microphotographs that separation of sympathetic ganglia from spinal nerves without injury to the spinal nerves is practically impossible because of the intimate association between the two. This evidence particularly refutes Popa's observations (78) on the pigeon, confirming Hunter, but it possibly may not apply to Hunter's observations; for if the sympathetic chain above the brachial plexus is an elongated ganglion, for which Popa (77) submits good evidence, then Hunter, instead of cutting the sympathetic fibers alone, would in reality be cutting a sympathetic ganglion (although possibly not completely destroying it).

If the influence of the sympathetic nervous system is not a primary one, the possibility of a secondary influence is quite plausible. Obviously, this

secondary influence would occur through a primary alteration in the circulation. No attempt was made by Hunter to control for this possibility of a circulatory change affecting tonus. Popa's work would seem further to indicate this possibility (77), for he found that the remote effect of sympathetic cutting in several birds-the immediate and continued effect being a loss of tonus-was an increased sensibility to cold, no doubt due to an altered circulatory state. The immediate effect of sympathectomy is vasodilation, and readjustment of the circulation in the region of vasodilation occurs only at varying periods after the disturbance. Tower (90) employed the phenomenon of increase in color and temperature in the dog's paw on vasodilation to observe the conditions of tonus under varying circulatory states. With this phenomenon available she could fairly easily judge the time of circulatory readjustment. After the period of readjustment equal circulation was found in both limbs in the resting state; but reflex vasodilation appeared in the normal limb on activity. In cases of parathyroid tetany, mild strychnine poisoning, and in possibly one case of decerebrate rigidity, she observed that the limb with poorer circulation(here the sympathectomized limb, since reflex vasodilation occurs in the normal limb) maintained a very slight state of hypertonus. Possibly, then, immediately after a sympathetic operation the the operated limb might appear relatively hypotonic to the slightly hypertonic normal limb. From these observations and from the fact that heat is a well-known therapeutic treatment for spastic conditions and contractures, Tower feels that, although her results were not extremely definite and consistent, observation and study of the effects of circulatory changes after sympathectomy are very essential. Immediately after sympathectomy, the general vasodilation in a limb might be so great that there would be the possibility of a stasis which would decrease the rate of removal of the waste products of

muscular activity. This would explain the observations by Popa (77), Coates and Tiegs (17), and Hunter, of a more rapid rate of fatigue in the sympathectomized muscle. The disappearance of this stasis on circulatory readjustment would make it easier to understand the failure of Campos, Cannon, et al (13) to observe any difference in performance between the operated and normal limb. But until we are sure of the appearance or non-appearance of fatigue under varying conditions of circulation, and until we have a better understanding of the direct relation between the sympathetic system and fatigue, it is wiser to be more conservative in interpreting these phenomena.

The necessity of sufficient control for trauma resulting from the operative procedure has already been discussed. However, still another control necessary is the one for possible unequal changes in tone as a result of labyrinthine and neck reflexes, as indicated by: Tower (90); Forbes, Cannon, et al (32); and Mortenson, Friedbacher, and Quade (71). It is well known that alteration in position of the neck can alter the degree of tonus: that is, by turning the neck so that the right ear approaches the ipsilateral shoulder, the limbs of the ipsilateral side show a condition of increased tonus; while those of the opposite side show a decreased tonus. It is also well known that the labyrinthine impulses influence tone; for an animal while lying on its back will exhibit full extension of all its limbs, a decrease becoming evident as it moves on its side (88). Most important, then, is a strict observance of symmetry of posture while an animal is lying on its back so that the effect of passive movements will be observed. Forbes, Cannon, et al have observed varying degrees of hypotonus and hypertonus in operated and normal limbs, which they attribute to labyrinthine and neck reflexes. The earlier workers were not so careful of this control, but Hunter (51) refused to admit the possibility of such an interpretation of his results, claiming

the use of proper controls of these vestibular and cervical phenomena.

The greatest support for the conclusion that the sympathetic has no direct effect on muscle tone comes from the inability of other workers to repeat the experiments. Only brief notes of their work will be made since their methods are similar to those of previous observers. Kanavel, Pollock, and Davis (55) using varying degrees of unilateral sympathectomy in eighteen cats with decerebration by cerebral anemia, could find no alteration in the rate of onset of rigidity, no difference in resistance to overcoming of the rigidity, and no difference in the lengthening and shortening reactions on normal and sympathectomized sides. To refute the criticism by Hunter that failure of confirmation of his work was partly due to insufficiency of time elapsing between sympathectomy and decerebration, Meek and Crawford (69) decerebrated dogs at varying periods after sympathectomy (from thirty-three to seventy-seven days). Still, by the usual methods, they could observe no difference in the tone or rigidity. The work of Sarah Tower (90) on dogs is especially noteworthy in that the greatest care was taken in the observance of controls: bilateral operation performed with unilateral sympathectomy, control against influence of neck and vestibular reflexes by symmetrical position of animal assured through suspension, equal left and right operations to prevent habitual one-leggedness, autopsies, discarding of improperly healed individuals, and observance of accompanying circulatory changes. Yet she was unable to confirm Hunter, either immediately after the operation or at the end of a long period. To duplicate more exactly Royle's experiment, Tower and Hines (91) observed normal gait, posture, and tonus thirty to sixty days after unilateral sympathectomy on goats, at which time decerebration was performed; but still they could not observe the differences observed by Royle. Mortenson, Friedbacher, and Quade (71) also working on goats, were unable to

confirm Royle; but observed sometimes a hypertonus on the operated side, sometimes a hypotonus, depending on position. Slightly varying the procedure Forbes, Cannon, et al (32), and Coman (27) found no variation on the sympathectomized side in postural reflexes in voluntary and in passive movements. Coates and Tiegs (17) were unable to confirm the whole experiment of Kuntz and Kerper (61), observing a great variation in flaccidity under light anasthesia (the procedure used by Kuntz and Kerper) and finding no sympathetic influence on the brake phenomenon, the knee jerk, tetanus rigor (developed by tetanus toxin), and decerebrate rigidity.

From the mass of non-confirming evidence in the repetition of Hunter's and Royle's experiments it must be concluded that there is insufficient foundation for the view that the sympathetic has a direct influence on tonus. It is safe to conclude that inference of sympathetic regulation of a reflex phenomenon requires an immediate lessening or disappearance of that phenomenon following removal of the sympathetic nerve supply. Failure of such lessening or disappearance to occur can only lead to the conclusion that any influence the sympathetic may have on skeletal muscle tonus is indirect.

Section 3.

Trophic Influence of the Sympathetic Nervous System.

A. Introduction.

From the foregoing discussion on the influence of the sympathetic nervous system on skeletal muscle tonus, the conclusion has been drawn that the sympathetic exerts no direct influence on this phenomenon. In fact, there are no positive grounds for assuming that the sympathetic has a direct excitant effect producing any mechanical change in skeletal muscle. Hartman, Evans, and Walker (43) claim that stimulation of a single muscle fiber with a strong current through the sympathetic produces vibrations and then twitchings; but this is more likely due to a spread of current to the somatic nerves. There is a description by Nakanishi (73) of alleged excitation and inhibition in skeletal muscle mediated by the sympathetic where the somatic supply of one gastrocnemius in the frog was cut and the sympathetic supply left intact; traction on the contralateral intact sciatic produced an improvement, and pinching of the ipsilateral eyelid produced an inhibition, of the muscle while weakly tetanized through its cut sciatic nerve. However, since this performance can be produced only once on the same animal, there is the strong possibility that the results, if they actually occurred, were produced by reflex circulatory change. Consequently, in view of the uncertainty of these experiments and in view of the observations by Schneider (86) that a strongly tetanized sympathetic has no effect on the latent period, on the progress of a single contraction, or on the action current of a normally acting skeletal muscle at any point of the contraction, it is evident that the sympathetic cannot produce direct mechanical change in the muscle.

There can be found, however, an early suggestion of the possibility of some other direct influence of the sympathetic on skeletal muscle, although at this moment the mechanism might seem slightly obscure. It has been observed (Cannon and Nice, 14) that stimulation of the splanchnics in cats, dogs, and rabbits produces an improvement in the contraction of fatiguing muscle, with a parallel rise in blood pressure - a slight improvement remaining after return of the blood pressure to normal - and that some improvement, long sustained, occurs when the blood pressure is kept constant. These adrenalin effects were duplicated by the injection of adrenalin, so that the authors conclude that adrenalin causes a direct improvement of muscular activity as well as an improvement of circulation. The confirmation of this direct adrenalin effect on intact and excised muscle (Gruber, 41) and the disappearance of Tiegel's contracture in the presence of adrenalin (Schäfer, 85), suggests a possible direct sympathetic action on skeletal muscle in the light of the sympathomimetic character of adrenalin activity.

B. The Trophic Implications of Orbeli's Observations.

The possibilities of a trophic function allocated to the sympathetic nervous system could hardly be termed idle speculation as a result of the observations of Orbeli and his pupil Ginezinsky (76)(37). Orbeli discovered that the contractions of a frog's gastrocnemius muscle, when fatigue is setting in through tetanic or single shock stimulation of the spinal nerve supply, is improved upon stimulation of the sympathetic trunk sending fibers to the muscle. Because the experiments took place in bloodless animals there could be no question of either circulatory or adrenalin effects initiating this phenomenon. As Orbeli points out, there is under sympathetic stimulation a close analogy between the response of the heart and that of skeletal muscle: a latent period between stimulation and beginning of gradual improved con-

traction in both; a sustained improvement after the sympathetic stimulation has been discontinued; and a more marked effect in fatiguing tissue. Consequently, Orbeli subscribes to the trophic interpretation of sympathetic action suggested by Pavlov (37), who feels that, in addition to the vasomotor and "functional" innervation to each organ, there is a trophic innervation regulating the metabolic changes occuring in the tissue.

There is no doubt that stimulation of the sympathetic without any intermediate circulatory change improves the contraction of fatiguing skeletal muscles, for the experiments and results have been duplicated by Labhart (62)(who obtained longer lasting recovery with single shock stimulation of the sympathetic fibers, 1 per second, than by tetanic stimulation, and who obtained a greater recovery with a lessening of frequency of stimulation of the somatic nerves than with stimulation of the sympathetic nerves), Michol (70), Maibach (67), Baetjer (3), Van Dijk (95), Corkill and Tiegs (84), and Charlet (16). However, the work of Baetjer alone will be elaborated with respect to this particular experiment, because it confirms Orbeli's results in circulation-intact animals. By plethysmographic records of the fatiguing muscles in cats stimulated through the sympathetic chain, it was observed that the contraction improved even with a slight vasoconstriction in the muscle (the only decrease in the height of contraction occurring in extreme cases of vasoconstriction), and also in cases with the circulation coming from a donor cat to prevent possible adrenalin effects.

In view of the wide confirmation of Orbeli's work, it is peculiar that Wastl (100) could not confirm the results on duplicating the experiment. Of course, it is difficult to comment on her attempts at confirmation in circulation-intact animals when there is no evidence of observation of attendant alterations in circulation. Bouman (8), too, was unable to confirm Orbeli's

results on employing the same technique, but he did observe that stimulation of the sympathetic improves contraction in skeletal muscle fatiguing as a result of submaximal stimulation of the somatic nerve supply rather than as a result of maximal stimulation of the somatic supply (the latter technique was employed by Orbeli). Thus, one may see that the early observations of Orbeli rest on a rather firm basis considering this absence of contradiction. There is the possibility that the improvement on sympathetic stimulation was the result of current spread to somatic nerves; but, as Maibach points out (67), there would then be no appreciable latent period between stimulus and the beginning of improvement.

C. The Possibility of Sympathetic Alteration of Resistance at the End Plate.

Before seeking evidence of actual trophic changes in the muscle it is well to discuss the possibilities of a sympathetic activity other than trophic, which might be the cause of relief of fatigue. Corkill and Tiegs (24) contend that sympathetic stimulation can only improve muscular contraction when the muscle is being fatigued through the nerve. It seems that when a frog's sartorius was fatigued directly by stimulation in the nerve-free end or by stimulation in a curarised preparation, sympathetic stimulation produced no improvement (as it did with the muscle fatigued through the nerve). This would place the seat of sympathetic action at the junction of the somatic nerve and muscle. Corkill and Tiegs allocate to this region the function of production of humoral substances which diffuse throughout the muscle to relieve fatigue.

There is, however, as Michol (70) points out, another interpretation. One can, if this is the seat of sympathetic activity, conceive of a relief of a fatigued condition at the end organ by a lowering of the resistance to passage of impulses from nerve to muscle, a change that would produce an improvement of contraction. To test this idea, Michol applied to the muscle

the purest form of curare known (ordinary curare gave confusing results), and found that sympathetic stimulation improved contraction in muscle fatiguing through direct stimulation. The experiment is convincing enough to suggest the conclusion that the sympathetic exerts its improving activity in the muscle itself. Furthermore, Michol believed that because single induction shocks (tetanic stimulation of nerve will alone elicit a response in muscle when the muscle is perfused with calcium-free sodium chloride) are not able to produce a response in muscle perfused with calcium-free sodium chloride solution when the sympathetic supply is stimulated, the sympathetic does not act in the region of the end organ, since it does not make possible the muscle response to sympathetic stimulation under these conditions. However, this evidence is not quite so convincing.

D. Trophic Changes in Skeletal Muscle After Sympathetic Stimulation or Sympathectomy.

The idea that the sympathetic can regulate or control directly the chemical changes in skeletal muscle is not a recent one. Nevertheless, the older investigators were more interested in the sympathetic control of chemical processes in its relation to muscle tone. In early investigations Ernst (30) and DeBoer (26) contend that tonus is produced through the slow burning of proteins in a sympathetically-controlled sarcoplasm, but their work is very unconvincing.

More significant are the results reported by recent workers. Büttner (12) reports in the frog an increase in lactic acid and glycogen after sectioning the rami communicantes. Hoffman and Wertheimer (49) feel that normal impulses traveling down the sympathetic fibers cause a decrease in glycogen, since they found in strychnine cramp that cutting the sympathetic chain results in the stopping of glycogen usage and, in normal animals, that warming or adrenalin

produces a decrease in glycogen. Of course, between the time of sympathectomy and muscle analysis there might be an alteration in circulation which might alter the composition of the muscle. This possibility is doubted by Britton (9) who found the decrease in glycogen after varying periods up to ninety days. However, we must not suppose that the operation results in a complete loss of glycogen (Herrin and Meek, 82; Dworkin, Bacq, et al, 29); but rather we should consider the sympathetic nervous system as a superimposed regulatory mechanism (Herrin and Meek, 82).

Whether sympathetic impulses produce an increase or a decrease in glycogen, or whether they produce an increase in creatin phosphagen (Jacky,54), one possible interpretation of sympathetic trophic activity appears quite obvious. In some way, stimulation of the sympathetic nerve fibers seems to result, under certain conditions, in an acceleration or catalyzing of either the synthesis of energy-producing compounds for muscular contraction or the decomposition of these compounds with the freeing of this energy. That this sympathetic effect is apparent only on superadded stimulation of the fibers in fatiguing muscle, suggests a relationship to Cannon's emergency hypothesis; but it is not well to speculate so freely when the knowledge of sympathetic control of trophic changes is so slight.

If it is a fact that sympathectomy produces a decrease in glycogen in the muscle, it offers a very interesting possible interpretation of the effect of sympathectomy on muscle action currents. Langelaan (64) found a consistent decrease in the demarcation currents of various frog muscles on sympathectomy. Also, Haller (42) discovered a lessening of frequency, briefer periods, and a weakening in the action currents of a frog's gastrocnemius after sympathectomy. It can be reasoned that, with the decrease in glycogen as a result of sympathectomy, there will be less energy available on glycogen breakdown for

the resynthesis of phosphagen, and that eventually there will be less phosphagen breaking down. To quote Ritchie (81): "The usual view of the excitation process and its transmission in nerve (and presumably, in muscle) is that it consists in the depolarization of a membrane, which at rest is kept polarized. In this process, energy is liberated and the subsequent repolarization process involves the performance of work by the cell at the expense of exothermic chemical reactions. The breakdown of phosphagen is supposed to be the first of the exothermic reactions in muscle.....and is likely to provide the immediate source of energy for repolarization." A lessening in the available phosphagen would then probably lower the degree of repolarization, and weaker action currents would result.

The question naturally arises as to what property of the sympathetic nervous system makes possible these changes, if they do occur. Of course, we are not certain that these are the direct results of sympathetic influence; in fact, Fulton (36) thinks that substances produced at the nerve endings (sympathetic) act as buffer substances, protecting the muscle against acid-metabolite increase, an important factor in fatigue production. Cobb and Wolff (21) do point out that the production of humoral substances upon sympathetic stimulation in smooth and cardiac muscle might suggest the factors involved in sympathetic trophic activity. Loewi (66) has found that excitor and depressor substances are formed in a perfusate through the heart of a frog on stimulation of the sympathetic and vagus nerves, respectively. Cannon and Bacq (15) discovered the production of a similar excitor substance in smooth muscle. More recently Tschannen (93) has reported that the production of the vagal substance in the frog's heart is not quite so certain, but he does affirm the presence of the excitor substance. The work on these humoral substances is so extensive that only brief notes of the results have been

sketched. However, it does seem that there might also be production of such substances in skeletal muscle to carry on the functions indicated. Even without direct sympathetic innervation to skeletal muscle fibers, these substances could be produced in the walls of the blood vessels, diffusing back into the tissue to produce their effects.

With the shortage of positive evidence, the possibilities with respect to trophic activity of the sympathetic nervous system are unlimited: consequently any explanation is unsatisfactory. However the data available indicate that the sympathetic nervous system probably has a greater influence on skeletal muscle than that previously attributed to it.

Section 4.

Influence of the Sympathetic Nervous System on the

Anterior Lymph Hearts of Rana Pipiens.

A. Introduction.

In the Salientia, as described by Gaupp (39) and Allison (2), there are two pairs of lymph hearts, an anterior pair being found on either side of the vertebral column, each organ resting on the dorsal surface of the transverse process of the third vertebra just beneath the posterior part of the scapula, and a posterior pair lying more superficially in the ischiadic region. A particularly interesting fact associated with the anatomy of the lymph hearts, whose walls are profusely supplied with blood capillaries, is the presence in each wall of a layer of striated muscle fibers, the fibers being collected in bundles which anastomose to form a network. The presence of a spinal nerve supply is certain, each anterior lymph heart receiving its supply from the R. intertransversarius ventralis of the third spinal nerve (Gaupp (39)).

The function of the lymph hearts is to propel lymph into the blood stream, by way of the venous system. The lymph is collected from the numerous lymph spaces, and the anterior hearts return the lymph to the blood by way of the vertebral vein. Conklin (23) has recently demonstrated the importance of the hearts in returning proteins to the blood stream; and Isayama (53) has estimated that the total blood volume passes through the lymphatic system of frogs fifty times in twenty-four hours. From this it is not at all difficult to realize the functional importance of the lymph hearts.

These organs are peculiarly suited to the study of sympathetic influence on skeletal muscle, because of their continuous rhythmic activity, the result

of periodic stimulation from somatic spinal centers. Brucke and Umrath (10) compare the spinal cord centers of the lymph hearts with the respiratory center because of period propagation of impulses down the nerve - a fact that they determined by a study of the action currents in the lymph heart nerve whose periodicity was duplicated by the action currents in the lymph heart itself. But these centers in the cord appear to be wholly automatic; for the same workers (11) could find no alteration in the action currents of the spinal nerve supply after section of the dorsal roots, the occurrence of which might have indicated the dependence of the center upon afferent impulses from the lymph heart itself. However, the actuating centers in the cord are independent for each member of a pair of hearts, anterior or posterior, since the contralateral hearts do not beat in unison as has long been known. Coupled with this independence of contralateral hearts is the recent evidence of central nervous coordination of the homolateral centers (Pratt and Reid, 79), as shown by the synchronism of lymph hearts on the same side of the body.

In the use of this particular organ for the study of sympathetic influence on skeletal muscle, another distinguishing characteristic must not be overlooked. The removal of spinal nerve supply to the lymph heart results in only a temporary loss of activity; for the heart resumes its beating, although with an initial tendency toward periodicity (45) (80). This replacement of neurogenic by myogenic activity occurs, as shown by Reid's recent work (80), even in transplanted hearts having no nervous connections.

There seems to have been no actual evidence of a sympathetic supply to the lymph hearts. Waldeyer (97) claimed the presence of ganglion cells in the region of the lymph hearts apparently related in some way to sympathetic fibers, and to these he assigned the responsibility for certain peculiarities of response (98). Hermann (45) found no alteration in rate on the removal of

part of the sympathetic chain. In spite of the meagerness of evidence, the rich blood supply to the lymph hearts would seem indicative of some form of sympathetic supply to these organs. The experiments here reported have been directed toward a clarification of the problems thus involved.

B. Method.

The experiments were performed on specimens of Rana pipiens of medium size, although two experiments were on Rana catesbeiana. The two sympathetic chains run on either side of the vertebral column, following closely the dorsal aorta and its arches. For the operation, that portion of the chain in the region of the III spinal nerve was selected for removal since the somatic nerve supply to the lymph heart arises from a branch of the III spinal nerve. In this particular region, the III sympathetic ganglion is directly ventral to the III nerve, connected with it by a short ramus communicans. In frogs the IV spinal nerve runs parallel and very close to the III spinal nerve, so that the IV sympathetic ganglion is separated from the III ganglion by a very short length of chain.

Two methods of approach were employed in the operative procedure for removing sections of the sympathetic chain, namely a ventral and a dorso-lateral, with the latter proving the more practicable. In every case but one, where nembutal was used, the animals were lightly anesthetized with ether for the sympathectomy and for the subsequent lymph heart observation; and aseptic methods were employed in the operations. In the few early operations, where the ventral approach was used, a small triangular incision was made posterior to the coracoid on one side, and the fibers of the oblique and pectoralis muscles were separated carefully with fine forceps. The remainder of the operation was performed under a dissecting microscope. In order to

find the III nerve, fine forceps were moved anteriorly, dorsal to the coracoid, and the lung was lowered medially and ventrally. The III nerve, when located, was traced centrally until the sympathetic chain was observed, whereupon the chain was cut and the incision closed. Too often, however, by this method considerable loss of blood occurred through hemorrhage; and since the parts of the chain could not be clearly viewed, the location of the sympathetic-chain section was never consistent.

The dorsolateral method of approach in the operation for removal of the possible sympathetic supply to the lymph heart was used in all other experiments because as a rule only slight subcutaneous bleeding occurred, and because the sympathetic chain from the II to the VI ganglia was entirely visible, permitting consistent removal of the same regions. With the animal placed on the frog board partly on its dorsal and partly on its lateral surface, a small incision was made just posterior to the scapula near its dorsal border. Under a dissecting microscope, the oblique and latissimus dorsi muscle fibers were separated and the peritoneum pierced. With fine forceps, the sympathetic chain was traced along its course (dorsal to the lung and accompanying the aortic arch) to the III nerve. In most instances, the III sympathetic ganglion with its ramus communicans, and small portions of the chain anterior and posterior to the III ganglion, were removed; the incision was then closed. This degree of operation was found sufficient to produce the results observed. It was thought that possibly some sympathetic fibers to the heart might travel in the IV spinal nerve, and for this reason, in several experiments, the IV nerve was cut; but this procedure produced no greater modification of the normal lymph heart activity than that which arises from the uncomplicated method. In one experiment the IV spinal nerve was cut bilaterally, with the sympathectomy only unilateral, in order that it might

be observed if, in the attempt to remove possible sympathetic supply to the lymph heart traveling by way of the IV spinal nerve, somatic fibers supplying some of the muscle fibers of the heart were destroyed. This event would probably be demonstrated in a partial contraction of both lymph hearts. In several experiments, bilateral operations accompanied by somewhat equal mechanical disturbances, with unilateral sympathectomy, were performed to control for the possible effect on lymph hearts of operative trauma. At the conclusion of the experiment, autopsies were made in order that the actual extent of the operation could be determined.

The lymph hearts were exposed for observation after periods varying from one hour to thirty days after the operation. After the frog was lightly etherized, it was fastened to a board with the dorsal surface uppermost. A midline incision was made between the scapulae; and the scapulae, or strictly, suprascapulae, were made free at their anterior, posterior, and medial borders by cutting the levator scapulae, rhomboideus anterior, rhomboideus posterior, and serratus superior muscles, together with any restraining fascia. To maintain the scapulae in a vertical position, hooks attached to the side of the board by elastic bands were placed near the anterior borders of the scapulae (in this position they lessen to some extent the tension on the lymph hearts). In this abnormal position the altered relationship of the scapulae and their musculature to the lymph hearts produces considerable tension on the hearts and their efferent vessels. For this reason the subscapular muscles were transected to relieve the tension exerted. In most of the experiments the lymph hearts were studied under a dissecting microscope, and this made possible the careful removal of fascia covering the hearts. Throughout the experiments the hearts were constantly moistened with Ringer's solution to prevent drying of the tissues.

In addition to the determination of the effect of sympathectomy upon lymph hearts by direct observation, kymographic records of the normal and sympathectomized hearts were obtained in most of the experiments. Light vertical straws resting on the lymph hearts were connected with straw writing levers of equal length, at equal distances from the fulcrum. During an experiment the position of the vertical straws on the lymph heart was often changed in order that a recorded difference in amplitude of the two lymph hearts might not be due alone to the position of the straws. On several occasions, the writing levers and vertical straws were reversed in the same experiment, the purpose of this being a control for possible differences in inertia of the two writing levers.

C. Results.

It is well to state at this point, that the results noted here are not those of completed experimentation, and that experiments are being conducted to check and elaborate these inconclusive data.

The first observations to be described are those made on lymph hearts one to thirty days after the sympathetic operation, for they show definite evidence of a sympathetic influence on the activity of lymph hearts. There were fourteen experiments performed whose results agree as to the alteration in activity of a sympathectomized lymph heart. The nature of this change was a slight but very noticeable decrease in amplitude of the beat, or better described, a decrease in the extent of excursion of the operated organ. Of course, the latter description is more complete for it indicates that removal of the supposed sympathetic supply to the lymph hearts apparently produces a weakening in the power of contraction. This weakening in power of contraction may be observed in Figures 1. and 2. Reversing the

writing levers or shifting the postion of the vertical straws in no case brought about a disappearance of this difference in power of contraction.

There was, however, some contradictory evidence. In one experiment, where nembutal was used as an anesthetic, no difference in the vigor or power of contraction could be observed three days after the operation. On autopsy, it was found that the operation , employing the dorsolateral method of approach, had removed the usual parts of the sympathetic chain. In one other experiment, where a correct operation had also been performed, the equal vigor of the two lymph hearts was not considered to be an important contradiction of earlier observations, for the frog was in a badly diseased condition. Nevertheless, two other experiments offered contradiction to the already stated evidence of a sympathetic influence on lymph hearts which suggests a very interesting interpretation. In these experiments, it was found that the III sympathetic ganglion was intact bilaterally and that the sympathetic chain was unilaterally cut posterior to the III spinal nerve in one animal and anterior and posterior to this nerve in the other. This observation suggests that removal of the sympathetic influence on lymph hearts is only secured by a removal of the III sympathetic ganglion or by a cutting of the ramus communicans of this ganglion. Attempts to dispute the evidence of sympathetic influence by bilateral operative procedure with unilateral sympathectomy and by unilateral operation without sympathectomy were unsuccessful in two experiments. Furthermore, in one case bilateral cutting of the IV spinal nerve with unilateral sympathectomy, resulted in a decrease in the power of contraction of the sympathectomized lymph heart alone. This last experiment failed to contradict the conclusion of a sympathetic influence on lymph hearts drawn from other experiments where unilateral sympathectomy was accompanied by ipsilateral sectioning of the

of the IV spinal nerve, a contradiction which would have suggested the possibility of the production of the apparent sympathetic effect by injury of part of the somatic nerve supply to the lymph heart.

As stated in the introduction to this section, the lymph heart wall has a very rich blood supply. Especially, since the wall is so thin, one would expect a very noticeable effect of circulatory change in this organ. For this reason two experiments were performed, designed for observation of the effect of removal of the circulation on lymph heart activity; one, in which the circulation was temporarily checked by clamping the aortic arches near their point of origin, with subsequent restoration of the circulation; and the other, in which the circulation was permanently removed by systemic cardiectomy. The results of removal of the blood supply by clamping off the aortic arches may be seen in Figures 2, 3, and 4. In Figure 2 the record is standard, that is , indicating the difference existing in power of contraction of the two lymph hearts before the circulation was checked. Figure 3 demonstrates the alteration produced upon removal of the blood supply. As can be seen, the difference in extent of excursion or amplitude of beat persisted, although there had been a decrease in frequency and form of beating (the change in frequency and type of beating is probably caused by the absence of blood supply to the central nervous system). The blood supply was kept from the lymph hearts for one hour and fifteen minutes, the same difference being observed throughout the entire period. Yet, when circulation was restored by removal of the aortic clamps (Figure 4), the original record (Figure 2) seems almost to be duplicated. In this animal, as in others,the decrease in extent of excursion of the sympathectomized heart resembled closely the type of contraction one would expect when a partial contraction took place through injury to some of the somatic nerve supply. However, from

Figure 1.
A - sympathectomized lymph heart
B-- normal lymph heart

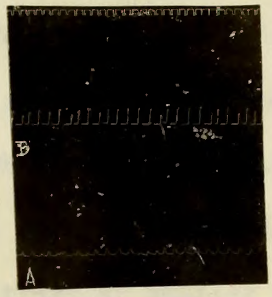

Figure 2.
A- sympathectomized lymph heart
B- normal lymph heart

Figure 3.
A - sympathectomized lymph heart
B - normal lymph heart

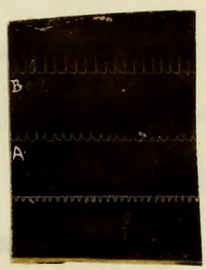

Figure 4
A- sympathectomized lymph heart
B- normal lymph heart

the results of an experiment previously described, it seems quite doubtful that injury to the IV spinal nerve is followed by partial contraction of the lymph heart of the same side.

Especially convincing were the results from the experiment on the effect of removal of the blood heart on the difference in activity of the two lymph hearts. The difference in activity persisted for twenty minutes after the systemic cardiectomy, at the end of which time an irregular form of beating of the sympathectomized heart set in, exhibiting at varying periods a single large beat in addition to very irregular smaller beats. The experiment on this frog took place one month after the sympathectomy.

In all the observations of lymph hearts made under the dissecting microscope (all but four), note was made of any obvious changes in the size of blood vessels surrounding the lymph hearts. Attempts to observe changes in caliber of the blood vessels in the walls of the hearts by alterations in color, were unsuccessful. As a rule there seemed to be no alteration in the size of surrounding vessels, but in a few cases a slight degree of constriction took place in the vessels of the operated side. If the efferent vessel of the sympathectomized heart were constricted to any marked degree, it might be suggested that a difference in fluid content and subsequently a difference in power of contraction of the lymph hearts would result from the resistance to the expulsion of lymph offered the operated heart by the constricted vessel. However, two experiments, one in which the efferent vessel of the normal heart was occluded, and one in which the efferent vessel of the sympathectomized heart was likewise occluded (both cases accidental) failed to produce any evidence in support of this possibility.

The evidence of sympathetic influence on the lymph hearts has been ob-

tained from frogs where the sympathectomy was performed at least one day before the time of observation (however, there has been only one observation made at this minimum interval). Of three experiments involving observation not more than one hour after sympathetic removal, two have offered no evidence of sympathetic influence, while one has definitely confirmed previous evidence. On all three animals, bilateral operations were performed with unilateral sympathectomy.

D. Discussion.

If the consistent results of the experiments dealing with the effect of removal of the circulation on the difference in power of contraction of normal and sympathectomized lymph hearts were more numerous, there would be little question of the direct influence of the sympathetic nervous system on the striated muscle of these organs. As it is, the definiteness of the results on the circulation experiments and the numerous confirmations of the differences produced by sympathectomy, suggest strongly the idea of direct sympathetic influence.

The inconstancy of the results in observations on frogs, carried on almost immediately after the sympathectomy, are difficult to interpret. The two observations which show no difference in beat after sympathectomy agree with a trophic interpretation of this sympathetic influence, since the removal of a superimposed regulatory mechanism of chemical processes would hardly produce immediately observable changes. Yet the other result, indicating an immediate result after sympathectomy, suggests the production of alterations in lymph heart activity by circulatory changes. This particular phase of experimentation needs further investigation.

The constant rhythmic activity of these striated muscle fibers requires rapid recovery from each contraction. It would seem then, that two important

aids in maintaining this high degree of activity would be an abundant circulation of the lymph heart and a sympathetic innervation acting directly and constantly on the striated muscle of the heart. The presence of an unusually abundant blood supply is quite evident. The effect of its removal apparently shows the necessity of intactness of the sympathetic nervous system to this high level of activity, but the mechanism of sympathetic regulation is not very obvious.

E. Summary.

1. Unilateral sympathectomy in *Rana pipiens* resulted, in fourteen cases, in a decrease in the power of contraction of the operated lymph heart.

2. The removal of blood supply to the lymph hearts, in two cases, did not cause a disappearance of the sympathetic alteration in power of contraction.

3. The possibility of a trophic influence on the lymph heart muscle is suggested.

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